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Heavy metal content and health risk assessment of commonly patronized herbal medicinal preparations from the Kumasi metropolis of Ghana

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Running title: Heavy metal content of herbal medicinal products

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26 **Abstract**

27 **Purpose**

28 **To address the question of whether users of herbal products (HPs) are exposed to harmful**
29 **contaminants, we evaluated six HPs mostly patronized in Kumasi for heavy metal**
30 **contamination and assessed the health risk associated with their use. This study is one of the**
31 **first safety evaluation studies on finished multiherbal products in the region.**

32 **Method**

33 Three antimalarial, two antidiabetic and one antihypertensive HPs were selected after a mini-survey
34 and coded randomly as HP A-F. The HPs were acid digested for quantitative analysis of heavy metals
35 using Inductively Coupled Plasma Mass Spectrometer. Hg quantification was carried out using cold
36 vapour atomic absorption spectroscopy.

37 **Results**

38 The cancer risk estimation values for the carcinogenic metals ranged between 1.54×10^{-9} to 3.73×10^{-4}
39 and were all within acceptable limits. The non-cancer health risk evaluation revealed that, some of
40 the products pose health risk to consumers. The estimated daily intake (EDI) for As in HPF was
41 2.48×10^{-4} mg/kg/day compared to the reference limit of 1.67×10^{-4} mg/kg/day. HPF also had high
42 hazard index (HI) of 5.70 (HI >1) in children as compared to 1.68 (HI >1) in adults showing a 3.4
43 folds increase in the health risk among the former.

44 **Conclusion**

45 The six polyherbal products exhibited carcinogenic risk within acceptable limits. Although, the non-
46 carcinogenic risk assessment of products HPA to HPE suggests safety, this can only be ascertained

47 after further characterization of their health risks in detailed chronic toxicity studies. The high HI for
48 product HPF suggests health risk for consumers of this product.

49

50 **Keywords:** Cancer risk, estimated daily intake, exposure, hazard index, hazard quotient, heavy
51 metals, herbal medicinal products, risk assessment.

52

53 **1.0 Introduction**

54 The use of Herbal Medicines (HM) for healthcare delivery dates back in centuries, and it is likely one
55 of the oldest methods of healthcare delivery in many parts of the world, [1]. HMs are used for
56 preventive, curative and chronic disease management. HM forms the fabric of the healthcare systems
57 in many low income and middle-income countries and has had an enormous contribution to the health
58 care system in Ghana. In recent years, the production and patronage of herbal medicinal products
59 (HMPs) in Ghana for therapeutic purposes have increased substantially, [2]. The WHO estimated that
60 close to 80% of the developing world's population rely on herbal medicine for their basic healthcare
61 needs, [3]. In the light of modern tools and technologies, HMs in Ghana have seen substantial
62 improvement in dosage form formulations, packaging and reported efficacies, [4]. Medicinal value
63 of these herbal preparations is usually due to the presence of essential phytochemicals such as tannins,
64 alkaloids, flavonoids and phenolic compounds that serve as active compounds in these medicinal
65 products, [5]. The phytochemicals are secondary plant metabolites produced and or stored for a
66 variety of reasons including defence and protection against pest and diseases. In addition to the
67 presence of active principle or compound(s), the herbal mixture may contain foreign toxic substances
68 including pesticides and heavy metal residues which may cause a health risk to human systems and
69 animals, [6].

Elevated heavy metal levels in medicinal plants have been associated with plants exposed to heavy metal polluted waters, the use of pesticides and other agrochemicals, plants growing along heavy traffic ways, previous dump-sites and near mining arrears, [7, 8]. When the herbal medicinal plants are processed into herbal preparations and consumed by humans, the heavy metal contaminants enter into the human system and cause health problems, [5]. It is believed that herbal medicine is one of the commonest modes of human exposure to heavy metals. Heavy metal intake through herbal products should, therefore, be regulated to avoid excessive build-ups in humans, [5, 6]. Though Ghana's Food and Drugs Authority (FDA) has been charged with controlling commodities for human use including herbal products and the organization is doing its best. Many HPs still enters the market without FDA registration and or without pre-market and post-market safety data. The FDA is also unable to carry out regular post-market surveillance of HPs on the market probably due to resource strength compared to the huge HPs on the market resulting in data gap. There is, therefore, a call for regular monitoring and surveillance studies to protect the health of the general public.

The increased use of agrochemical such as pesticides in Ghana to fight pest has increased the risk of heavy metal contamination these days and poses a health risk. The surge in the use of mercury and arsenic for small-scale illegal gold mining operations popularly known as 'galamsey' in the country in recent years is a major health concern both to policymakers and public health professionals. The heavy metals may finally end up in the tissues of these higher medicinal plants and into humans through the herbal preparations. Recently, waters near the Obuasi and Takwa gold mines in Ghana were found to be contaminated with heavy metals, [7, 9]. Some foodstuffs [10] and tea products [11] were also found to be contaminated with heavy metals and unsafe for consumption. Mutations in the genetic material, cancer, central nervous system disorders, liver and kidney toxicities are among the reported health problems associated with heavy metals [5]. **As, Cd, Pb and Hg** are among the most toxic metal contaminants based on previous reports, [12, 13]. Lead poisoning causes abdominal pain,

95 severe anaemia and haemoglobinuria [5] and arsenic poisoning may cause skin lesions, cancer
96 [12], diabetes and lung disease [14, 15]. Mercury poisoning has been associated with cardiovascular
97 problems, neuropathy, tremors, nephrotoxicity, immunotoxicity, carcinogenicity and death, [13,
98 16]. Cadmium, on the other hand, has been associated with increased risk of hormone-dependent
99 cancers including endometrial cancer [17], nephrotoxicity, skeletal damage and cardiovascular health
100 problems, [18].

101

102 Due to methodological challenges and the complex nature of multi-herbal mixtures, researchers shy
103 away from it until recently resulting in a paucity of data concerning multi-herbal preparations on the
104 market. There is also the lack of pre-market and post-market safety and quality control data on most
105 certified and uncertified herbal medicinal products on the Ghanaian market, [19]. The present study,
106 therefore, determined the presence of heavy metal contaminants in six commonly used herbal
107 medicinal products in Kumasi metropolis of Ghana and evaluated the health and cancer risks
108 associated with their consumption.

109

110

111 **2.0 Method**

112 **2.1 Sample selection**

113 A mini survey was carried out among some randomly selected herbal medicine users and pharmacy
114 shops that also sell herbal medicine on wholesale or in retail. The mini survey was carried out in
115 Kejatia, Bantama and Ash-town districts in the Kumasi Metropolis. Herbal medicine users were asked
116 about the anti-malarial, anti-hypertensive and anti-diabetic herbal medicinal products they go for
117 when unwell. Also, the wholesale and retail pharmacy shops involved in the study were asked about
118 the most patronized antimalarial, anti-diabetic and anti-hypertensive HMPs in their collections.
119 Participation in the interview was entirely voluntarily, interviewees were free to opt out of the study

120 at any time, no minors were involved in this study and the minimum age of the participants was over
121 20 years. To partake in this mini-interview, the herbal medicine user needed to be at least 18 years
122 and over and gave their consent and wiliness to part take in the study. Participants were asked not to
123 give any identification numbers or their family names during the short interview. The list was
124 compiled and tallied. The top 3 antimalarial (fig. 4A), top 2 anti-diabetics (fig. 4B) and the top 1 anti-
125 hypertensive (fig. 4C) were selected for the heavy metal study. The six HMPs were randomly coded
126 for ethical reasons and henceforth shall be represented by their random codes; HPA, HPB...HPF.

127

128 **2.2 Wet di-acid digestion of the herbal products (HPs)**

129 For the herbal preparations wet di-acid digestion comprising of nitric acid (HNO_3) and perchloric
130 acid (HClO_4) digestion method was employed, [20 - 22]. Measurements were made in triplicate and
131 the averages were reported.

132

133 **2.3 Agilent ICP-MS 7700 series heavy metal and elemental analysis**

134 Heavy metals and trace elements present in the digested herbal samples were analyzed using
135 Inductively Coupled Plasma-Mass Spectrometer (ICP-MS); Agilent ICP-MS 7700x (Agilent
136 Technologies, Inc. Hachioji-shi, Tokyo, Japan). Analytical grade calibration standards solution and
137 blank were run prior to sample injection. All solutions used were of analytical grade. The ICP-MS
138 7700x has high detection power, [23-24] and the obtained results were in parts per billion (ppb) and
139 the final results were obtained by calculating back into the undiluted solution. The Pb, As, Cd, Cr,
140 Cu, Ni, and Mn content in the HMPs were determined using this ICP-MS instrument and standard
141 method for metal analysis with this instrument was followed.

142

143 **Instrument conditions and quality control**

144 The instrument was rinsed with water and recalibrated after every ten runs. Linear analytical range
145 (LAR) standards of known concentrations (cal zero, 25 ppb, 50 ppb and 100 ppb) of each metal were
146 used as external standards. The analysis was first carried out in no gas mode (without the introduction
147 of He gas). It was repeated in a gas mode (He gas was introduced) due to the polyvalent metals like
148 Cr. The detector was set at analogue mode during the no gas mode analysis, but the detector was set
149 at pulse during the gas mode analysis. The recovery for the standards of Cr, Pb, As, Cd, Mn, Cu and
150 Ni were between 91% and 108%. The relative standard deviations between replicate analyses were
151 all less than 6%. Continue calibration verification standard (CCV) of 25 ppb was run after every 10
152 samples and at the end of every sequence. The measured CCV values ranged from 23.0 ppb to 27.31
153 ppb (within $\pm 10\%$). The quality control parameters of all steps of validation proved the accuracy of
154 the results, [23-25]. The limit of detection (LOD) for Cr, As, Cd, Mn, Pb, Cu and Ni was 0.004 ppm.

155

156 **2.4 Mercury analysis with cold vapour atomic adsorption spectrometer (CV-AAS)**

157 Mercury analysis and quantification was carried out on cold vapour atomic adsorption spectrometer
158 Varian SpectrAA.240FS (Varian Inc, California, USA) equipped with cold vapour generation
159 accessory (VGA-77) using the cold vapour technique. Mercury in the digested sample was reduced
160 to elemental mercury using SnCl_2 solution as reductant and deionized water as an acid to cold vapour
161 VGA system. Freshly prepared Hg standard solution (1 mL/L) was made by appropriate dilution and
162 used for prepared working standard solution, [26-27]. Standard samples and blanks were analysed
163 following the same procedure. The system plots calibration curve for the standards which it uses to
164 determine the Hg content in the diluted sample. The final concentrations were obtained by calculating
165 back the Hg concentrations in the original samples.

166

167

168 **Instrument conditions and quality control for Hg**

169 The Varian SpectrAA.240FS cold vapour atomic absorption spectrometer equipped with autosampler
 170 was set at automix sampling mode for mercury analysis. Measurements were done as described before
 171 [26-28]. The peak height measurement mode was used for the analysis. Measurements were carried
 172 out in triplicate. Smoothing was set at 10 points and reading was done at 253.7 nm with a slit width
 173 of 0.5R nm and a lamp current of 4.0 mA. Gain for the analysis was at 83%. Standards of 10 µg/L,
 174 20 µg/L and 50 µg/L were used. Re-slope rate was 500 with 2 re-slope standards. Re-slope lower
 175 limit was 85% and the upper limit was 115%. Calibration algorithm was set to linear with a lower
 176 calibration limit of 75% and an upper calibration limit of 150%. Measurement time was 5.0 seconds
 177 with a pre-read delay of 45 seconds. The relative standard deviation between replicate analyses ranged
 178 from 2.3% to 4.4 %. The 'r' value was 0.9998. The linear absorption equation for the estimation of
 179 analyte concentration (C) was

$$180 \quad \text{Abs} = 0.01731 * C + 0.01271 \dots\dots\dots (1)$$

181 Where Abs is the sample absorption at 253.7 nm wavelength.

182

183 **2.5 Health risk assessments**

184 **2.5.1 Estimated Daily Intake of the heavy metals**

185 The estimated daily intake (EDI) of each heavy metal (Cr, Mn, Ni, Cu, As, Cd, Pb and Hg) present
 186 in the mixture was determined by the following equation [29, 30];

$$187 \quad EDI = \frac{E_D \times C}{W_{AB}} \dots\dots\dots (2)$$

188 Where; EDI is the estimated daily intake of the heavy metal, C is the determined heavy metal
 189 content in the HP, E_D is the daily dosage of the HP and W_{AB} is the Ghanaian average body weight;
 190 (65 kg adults, 24 kg children), [30-31]. International oral reference dose values for the heavy metals
 191 RfDo ($\text{mg kg}^{-1} \text{ day}^{-1}$) used in this study were; 0.02 for Cr (VI); 0.14 for Mn; 0.02 for Ni; 0.001 for
 192 Cu; 0.003 for As; 0.001 for Cd; 0.004 for Pb and 0.0001 for Hg. The reference values as stated by

193 FAO/WHO (Codex Alimentarius Commission) [32], US EPA 2015 [33] and other published
 194 materials [27- 30, 34].

195

196 **2.5.2 Target hazard quotient for non-carcinogenic risk**

197 The equation below was used to estimate the targeted hazard quotient (THQ) of the non-
 198 carcinogenic effects of the heavy metals present in the herbal products.

$$199 \quad \text{THQ} = \frac{\text{EFr} \times \text{ED}_{\text{tot}} \times \text{IFR} \times \text{C}}{\text{RfDo} \times \text{BWa} \times \text{ATn}} \dots\dots\dots (3)$$

200 Where;

201 EFr (exposure frequency): Malaria incidence density of approximately 5 infections per person per
 202 year was considered for sub-Saharan African and for this study [35]. Anti-malarials: 5 malaria
 203 incidences a year and dosages as written on the product label were used. Anti-diabetic or hypertensive
 204 drugs are used as stated on the product label or throughout the year due to the chronic nature of the
 205 disease; 365 days a year and dosages as stated on the product label.

206

207 ED_{tot} (Length of exposure) was set to 65 years as the average for Ghanaian males and females based
 208 on the average life expectancy in Ghana, adult dose as stated on the product labels starts from age 12
 209 years (i.e. ED is 65-12 = 53 years) for HPA - HPE and from age 6 years (i.e. ED is 65-6 = 59 years)
 210 for HPF. IFR: Dosages as indicated on the product bottles (kg/person/day). C is the concentration of
 211 the contaminant metal/pesticide in the HMP (mg/kg). RfDo is the oral reference dose (mg /kg/day);
 212 BWa is the adult body weight (65 kg); ATn is the average exposure time for non-carcinogens can
 213 also be estimated as:

$$214 \quad \text{ATn} = \text{EFr} \times \text{ED}_{\text{tot}} \dots\dots\dots (4)$$

215

216 If the value of THQ is less than 1, then the exposed local population (consumers) is said to be safe.
217 But if THQ is equal to or higher than 1, is considered as not safe for human health, therefore poses
218 potential health risk, and related interventions and protective measurements should be taken.

219

220 **2.5.3 Hazard Index (HI)**

221 To estimate the risk to human health through more than one contaminant in a given product, the HI
222 has been developed by US EPA, 1989, [36-37]. The chronic hazard index (HI) is the sum of more
223 than one hazard quotient for multiple toxicants in the HP. It is believed that, exposure to two or more
224 pollutants may result in additive and/or interactive effects, [38]. Assuming the additive effects, THQs
225 can be summed across constituents to generate a hazard index (HI) for an oral dosage pathway
226 combination, [38].

$$227 \quad HI = \sum_{n=1}^i THQ_n \dots\dots\dots (5)$$

228

229 Where; THQ_n is the targeted hazard quotient for the nth term of contaminant, HI is the hazard index

230

231 **2.5.4 Cancer risk estimation**

$$232 \quad CR = CSF * EDI \dots\dots\dots (6)$$

233

234 Where, CSF is the oral carcinogenic slope factor of 0.0085 (mg/kg/day) ⁻¹ for Pb set by CalEPA
235 (OEHHA) [39] and 1.5 (mg/kg/day)⁻¹ for arsenic (As) set by US EPA [40]. EDI is the estimated
236 daily intake of heavy metals. Acceptable risk levels for carcinogens range from 10⁻⁴ (risk of
237 developing cancer over a human lifetime is 1 in 10,000) to 10⁻⁶ (risk of developing cancer over a
238 human lifetime is 1 in 1,000,000), [22, 25].

239

240 **Ethical clearance**

241 Study participants provided a written informed consent to participate in the study. Ethical clearance
242 for the study was issued by the University of Cape Coast Institutional Review Board (UCCIRB)
243 (ethical approval number: UCCIRB/EXT/2017/07).

244

245 **3.0 Results and discussion**

246 The internationally established legally permitted maximum residual limits (MRLs) were obtained
247 from the literature, [22, 32, 41-42]. The toxicant level above the established MRLs poses a health risk
248 to consumers and vice versa. It must be stated that chromium IV and VI have different toxicities and
249 MRL for chromium (VI) was used for this study due to its higher toxicity compared to chromium
250 (IV). In this study, all the measured chromium was assumed to be chromium VI with a similar reason
251 as above. In this study, the maximum residual content of Cr, Mn, Ni, Cu and As were above the MRL
252 in all the six herbal preparations (Table 1). This indicates that these metal contents are above the legal
253 limits to be on the market. Pb contents for HPC, HPE and HPF were also below the MRL. It must be
254 stated, however, that the MRLs are state or country dependent and vary from one state to the other.
255 MRLs are essential for legal purposes but not conclusive for health risk estimation due to differing
256 consumption frequencies, dosage variations and body weight differences.

257

258 Health risk estimation based on the estimated daily intake (EDI) of the heavy metal contaminant is
259 one of the vital health risk assessment tools. It takes into account the frequency and duration of
260 exposure and the body weight of the exposed persons. The EDI for Cr, Mn, Ni, Cu, As, Cd, Pb, and
261 Hg were all within the upper tolerable daily intake reference limits for HPA-HPE (Table 2). This
262 indicates that the daily intake of these herbal products poses no short to mid-term heavy metal health
263 risk to the public. The EDI for As was determined to be higher (2.48×10^{-04} mg/kg/day) than the upper
264 tolerable daily intake reference limit (1.67×10^{-04} mg/kg/day) for HPF. This indicates that consumers
265 of HPF are exposed to short-term to long-term arsenic health risk. Based on previous knowledge,

266 overexposure to arsenic is associated with risk of skin lesions, high blood pressure and diabetes
267 mellitus [43]. There is also an increased risk of cancer [44].

268

269 The herbal products do not pose long-term health risk per the metal considered if the Hazard risk
270 index (HRI) value is less than 1; and poses a health risk if the HRI is equal to or greater than 1.
271 HRI for non-carcinogenic effects measures the long-term exposure of the heavy metal contaminants
272 present in the herbal preparations. The HRI for Cr, Mn, Ni, As, Cd, Pb, and Hg, were all less than 1
273 (Table 3). This means that the consumption of these (HPA - HPF) poses no health risk due to these
274 metals. However, the HRI of Cu for HPF (1.68) is greater than 1. This indicates that long-term
275 exposure to HPF poses a health risk due to overexposure to copper. Copper is a microelement, but
276 overexposure to this essential mineral has been reported to predispose the consumer
277 to gastrointestinal mucosal ulcerations and bleeding, hepatic necrosis, coma, cardiotoxicity,
278 hypotension [45], leukaemia and cancer [46]. Cd and Hg contents, on the other hand, were well below
279 the MRL limits for all the 6 HPs.

280

281 It is known that an HI value less than 1 implies that the exposed population is unlikely to experience
282 any adverse health effect in their lifetime. However, if the THQ (Tables 4 and 5) is equal to or higher
283 than 1, [25, 47-48], there is a potential health risk to the exposed population and related interventions
284 and protective measures needed to be taken to protect the population. The HI values for HPA – HPE
285 were less than 1. This indicates the combined effects of the heavy metal contaminants present in a
286 particular herbal preparation poses no health risk in the long term for both adults (Fig. 2) and children
287 (Fig. 3). The HI for HPF was higher than 1 probably due to a high daily intake of Cu in this HP. This
288 poses the consumer Cu adverse health effects especially among children due to the very high HI value
289 (>4.5) (Fig. 3).

290

291 The total cancer risk was within the acceptable limits for all the studied herbal products (fig. 3).
292 Acceptable risk levels for carcinogens range from 10^{-4} (risk of developing cancer over a human
293 lifetime is 1 in 10000) to 10^{-6} (risk of developing cancer over a human lifetime is 1 in 1000000),
294 [35]. Values of CR lower than 10^{-6} are considered as negligible, above 10^{-4} are considered to be
295 unacceptable and lying in between 10^{-6} and 10^{-4} are considered an acceptable range, [35]. The cancer
296 risk estimation for As and Pb present in the six herbal products ranged between the values of 1.54×10^{-9}
297 (least) to 3.73×10^{-4} (highest) and were all within the acceptable limits. The total cancer risk due to
298 the sum total of risk presented by the individual carcinogenic metals presents per herbal preparation
299 was also all within the acceptable limit. This observation indicates that the consumption of these
300 herbal products does not pose any long-term cancer risk to the public.

301

302 **4.0 Conclusion**

303 The polyherbal products (HPA – HPF) evaluated in this study exhibited carcinogenic risk within
304 acceptable limits. The non-carcinogenic health risk assessment suggests that five of the products
305 (HPA to HPE) may be safe. However, this safety can be ascertained only when the health risks of
306 these products are further characterized in detailed chronic toxicity studies. The high HI recorded for
307 HPF, on the other hand, suggests increased health risks for consumers of this product. We advise,
308 therefore, that the use of these polyherbal products, especially HPF, should be done with much
309 caution. We also recommend that all relevant national and international agencies should be alive to
310 the responsibility of promoting public safety and global health by periodically reviewing and
311 enforcing existing policies regulating the herbal medicine industry.

312

313

314 **Note (N.B).:**

315 The manufacturers of the herbal products including HPF have been briefed with the findings from
316 this study. Recommendations were also made to the manufacturers to take steps in preventing metal
317 contamination and ensure good manufacturing practices.

318

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323

324 **Conflict of interest**

325 The authors declare that they have no conflict of interest in carrying out any part of this work

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469 **FIGURES AND TABLES**

470

471 **Table 1: Maximum heavy metal content (mg/kg) of the herbal medicinal products**

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	1.34427	3.34838	0.89544	8.32478	1.28474	0.0083	0.11961	ND
HPB	1.35674	3.33046	0.94961	8.13625	1.02657	0.00832	0.13969	0.00005
HPC	1.23508	3.92038	1.21877	8.78602	1.14446	0.00866	0.08068	ND
HPD	1.24268	2.28998	0.93383	8.57095	1.01004	0.00834	0.11712	0.002739
HPE	0.29191	0.84375	0.17287	1.75486	0.25989	0.00181	0.02338	ND
HPF	1.67602	2.82811	1.20886	9.171	1.35453	0.0083	0.0733	ND
MRLs	0.05	0.26	0.6	0.1	0.02	0.06	0.1	0.01

472 HPA-F: herbal product A-F; MRL: maximum residual limits; ND means not detected

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475 **Table 2: Estimated daily intakes (EDI) of the heavy metals**

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	4.77×10^{-5}	1.19×10^{-4}	3.18×10^{-5}	2.96×10^{-4}	4.56×10^{-5}	2.95×10^{-7}	4.25×10^{-6}	0
HPB	8.35×10^{-6}	2.05×10^{-5}	5.84×10^{-6}	5.01×10^{-5}	6.32×10^{-6}	5.12×10^{-8}	8.60×10^{-7}	3.08×10^{-10}
HPC	1.47×10^{-5}	4.67×10^{-5}	1.45×10^{-5}	1.05×10^{-4}	1.36×10^{-5}	1.03×10^{-7}	9.61×10^{-7}	0
HPD	8.99×10^{-6}	1.66×10^{-5}	6.75×10^{-6}	6.20×10^{-5}	7.30×10^{-6}	6.03×10^{-8}	8.47×10^{-7}	1.98×10^{-8}
HPE	2.26×10^{-6}	6.54×10^{-6}	1.34×10^{-6}	1.36×10^{-5}	2.02×10^{-6}	1.40×10^{-8}	1.81×10^{-7}	0
HPF	3.07×10^{-4}	5.19×10^{-4}	2.22×10^{-4}	1.68×10^{-3}	2.48×10^{-4}	1.52×10^{-6}	1.34×10^{-5}	0
Upper tolerable daily intake Reference limits								
CA HP (mg/kg/day)	3.33×10^{-4}	NA	NA	NA	1.67×10^{-4}	1.00×10^{-4}	3.33×10^{-4}	3.33×10^{-4}
WA (mg/kg/day)	8.33×10^{-4}	4.33×10^{-3}	2.33×10^{-2}	5.00×10^{-2}	3.33×10^{-4}	1.00×10^{-3}	1.67×10^{-3}	1.67×10^{-4}

476 CA is for Canadian upper tolerable daily intake reference limits for finish herbal products (HP) in mg/kg
477 (bw/day),¹ and 'WA' is for WHO/FAO (mg/kg bw/day)⁴².
478 HPA-F: herbal product A-F. NA means the upper tolerable daily intake reference limit for that particular
479 metal is not available from that authority/ body.
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Table 3: Hazard risk index (HRI) for HRI for non-carcinogenic effects

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	2.39×10^{-03}	8.49×10^{-04}	1.59×10^{-03}	2.96×10^{-01}	1.52×10^{-02}	2.95×10^{-04}	1.06×10^{-03}	0
HPB	4.17×10^{-04}	1.46×10^{-04}	2.92×10^{-04}	5.01×10^{-02}	2.11×10^{-03}	5.12×10^{-05}	2.15×10^{-04}	3.08×10^{-06}
HPC	7.35×10^{-04}	3.33×10^{-04}	7.26×10^{-04}	1.05×10^{-01}	4.54×10^{-03}	1.03×10^{-04}	2.40×10^{-04}	0
HPD	4.49×10^{-04}	1.18×10^{-04}	3.38×10^{-04}	6.20×10^{-02}	2.43×10^{-03}	6.03×10^{-05}	2.12×10^{-04}	1.98×10^{-04}
HPE	1.130×10^{-04}	4.670×10^{-05}	6.70×10^{-05}	1.36×10^{-02}	6.72×10^{-04}	1.40×10^{-05}	4.53×10^{-05}	0
HPF	1.54×10^{-02}	3.71×10^{-03}	1.11×10^{-02}	1.682	8.28×10^{-02}	1.52×10^{-03}	3.36×10^{-03}	0

484 HPA-F: herbal product A-F. The bolded value represents HRI value above the reference limit.

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488 **Table 4: THQ for adults using a body mass of 65 kg**

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	2.39×10^{-03}	8.49×10^{-04}	1.59×10^{-03}	2.96×10^{-01}	1.52×10^{-02}	2.95×10^{-04}	1.06×10^{-03}	0
HPB	4.00×10^{-05}	1.40×10^{-05}	2.80×10^{-05}	4.80×10^{-03}	2.02×10^{-04}	4.91×10^{-06}	2.06×10^{-05}	2.95×10^{-07}
HPC	2.12×10^{-04}	9.61×10^{-05}	2.09×10^{-04}	3.02×10^{-02}	1.31×10^{-03}	2.97×10^{-05}	6.92×10^{-05}	0
HPD	2.46×10^{-04}	6.48×10^{-05}	1.85×10^{-04}	3.41×10^{-02}	1.33×10^{-03}	3.30×10^{-05}	1.16×10^{-04}	1.09×10^{-04}
HPE	1.13×10^{-04}	4.67×10^{-05}	6.70×10^{-05}	1.36×10^{-02}	6.72×10^{-04}	1.40×10^{-05}	4.53×10^{-05}	0
HPF	1.54×10^{-02}	3.71×10^{-03}	1.11×10^{-02}	1.68	8.28×10^{-02}	1.52×10^{-03}	3.36×10^{-03}	0

489 HPA-F: herbal product A-F; THQ: targeted hazard quotient. The bolded value represents THQ

490 value above the reference limit.

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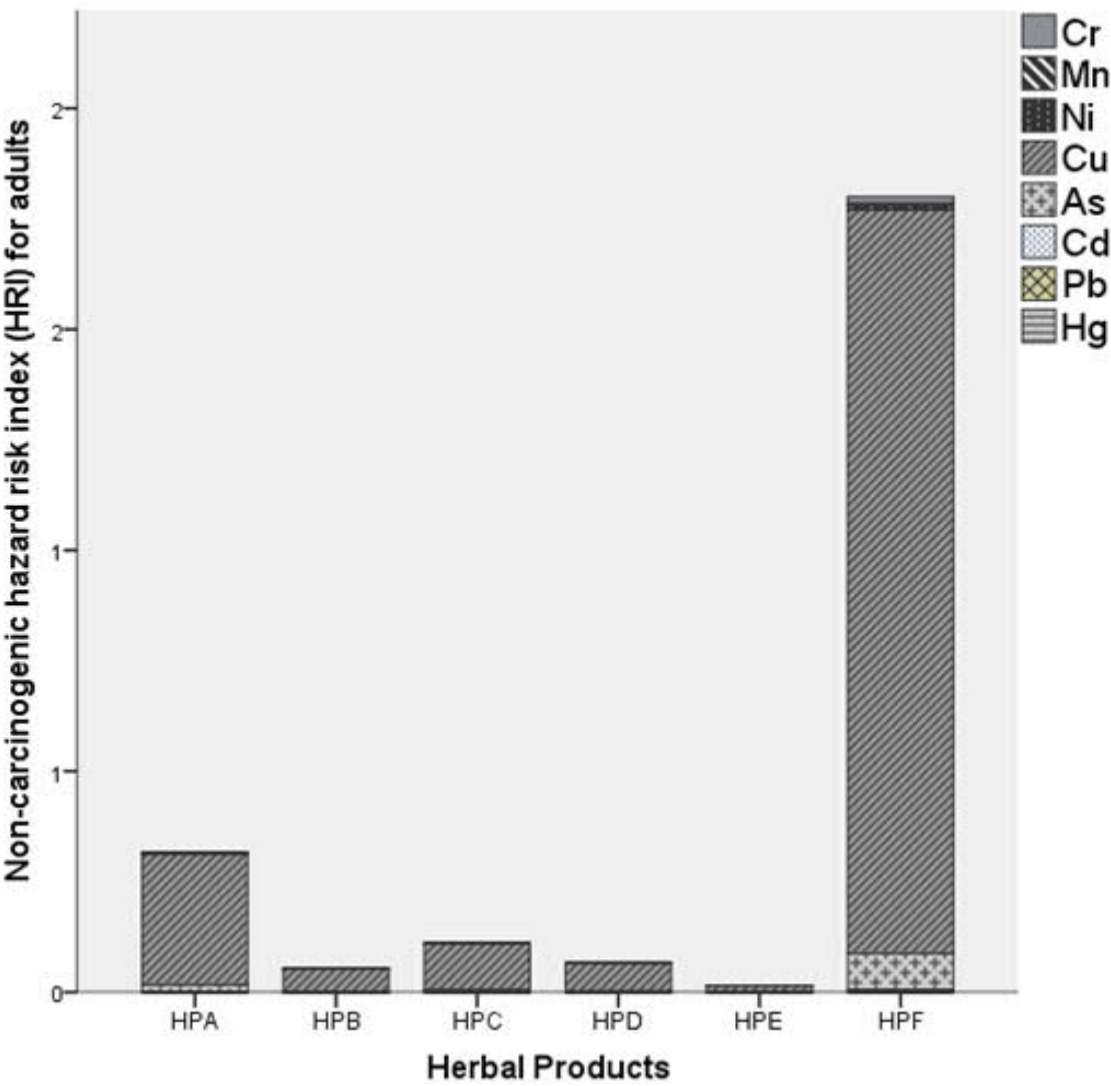
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494 **Table 5: THQ for kids using a body mass of 24 kg**

Sample	Cr	Mn	Ni	Cu	As	Cd	Pb	Hg
HPA	6.46×10^{-03}	2.30×10^{-03}	4.306×10^{-03}	8.01×10^{-01}	4.12×10^{-02}	7.98×10^{-04}	2.88×10^{-03}	0
HPB	5.42×10^{-05}	1.90×10^{-05}	3.79×10^{-05}	6.50×10^{-03}	2.73×10^{-04}	6.65×10^{-06}	2.79×10^{-05}	4.00×10^{-07}
HPC	5.73×10^{-04}	2.60×10^{-04}	5.65×10^{-04}	8.15×10^{-02}	3.54×10^{-03}	8.03×10^{-05}	1.87×10^{-04}	0
HPD	3.33×10^{-04}	8.78×10^{-05}	2.51×10^{-04}	4.60×10^{-02}	1.81×10^{-03}	4.47×10^{-05}	1.57×10^{-04}	1.47×10^{-04}
HPE	NA	NA	NA	NA	NA	NA	NA	NA
HPF	4.16×10^{-02}	1.00×10^{-02}	3.00×10^{-02}	4.56	2.24×10^{-01}	4.12×10^{-03}	9.10×10^{-03}	0

495 HPA-F: herbal product A-F; THQ: targeted hazard quotient; NA: not applicable, for the product
 496 'HPE' is not administered to patients below 12 years.
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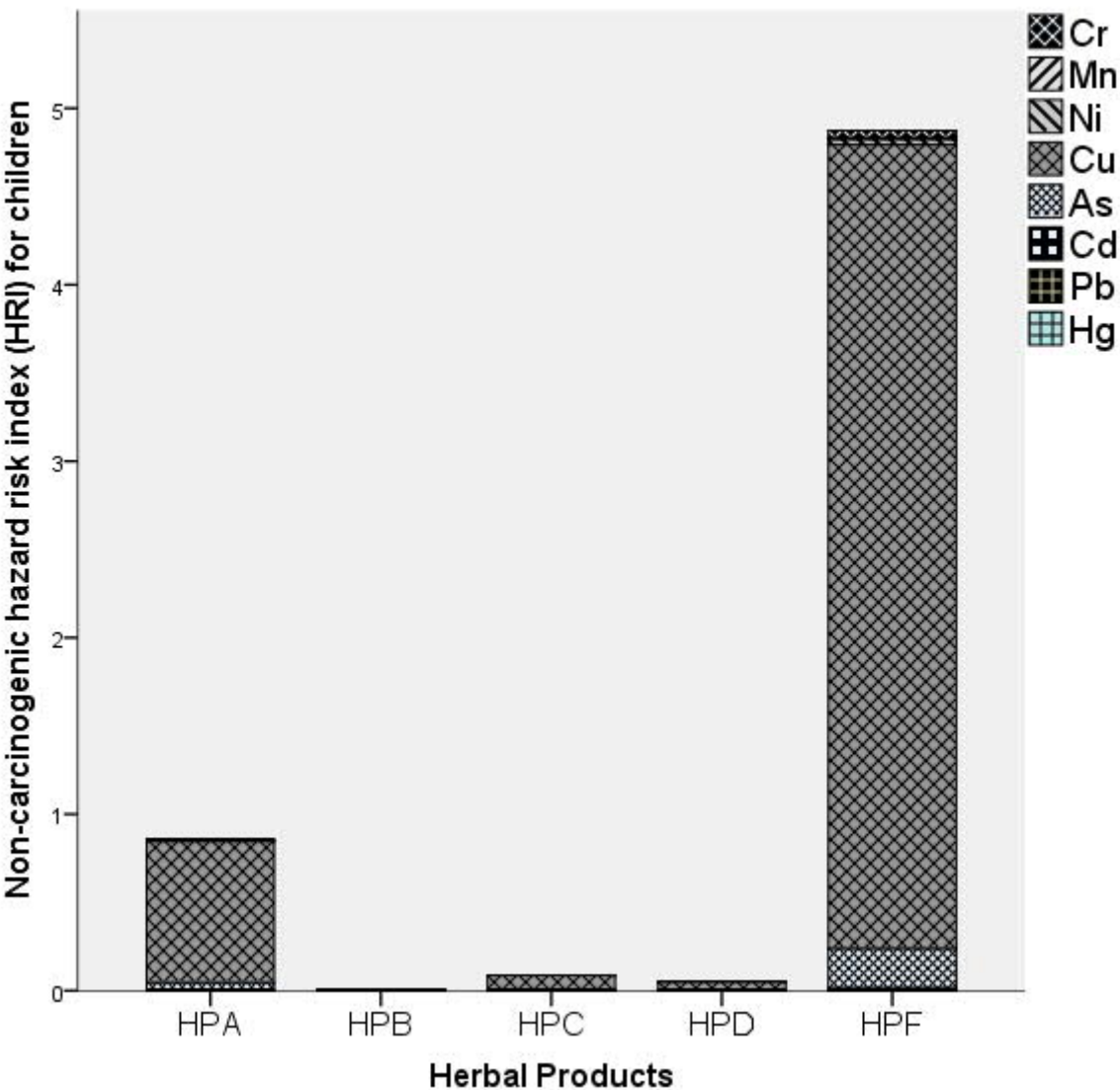


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Figure 1: Chronic Hazard Index (HI) for adults.

HPF has HI value for adults greater than 1.

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508 **Figure 2: Chronic Hazard Index (HI) for Kids.**
509 HPF has HI value for kids greater than 1

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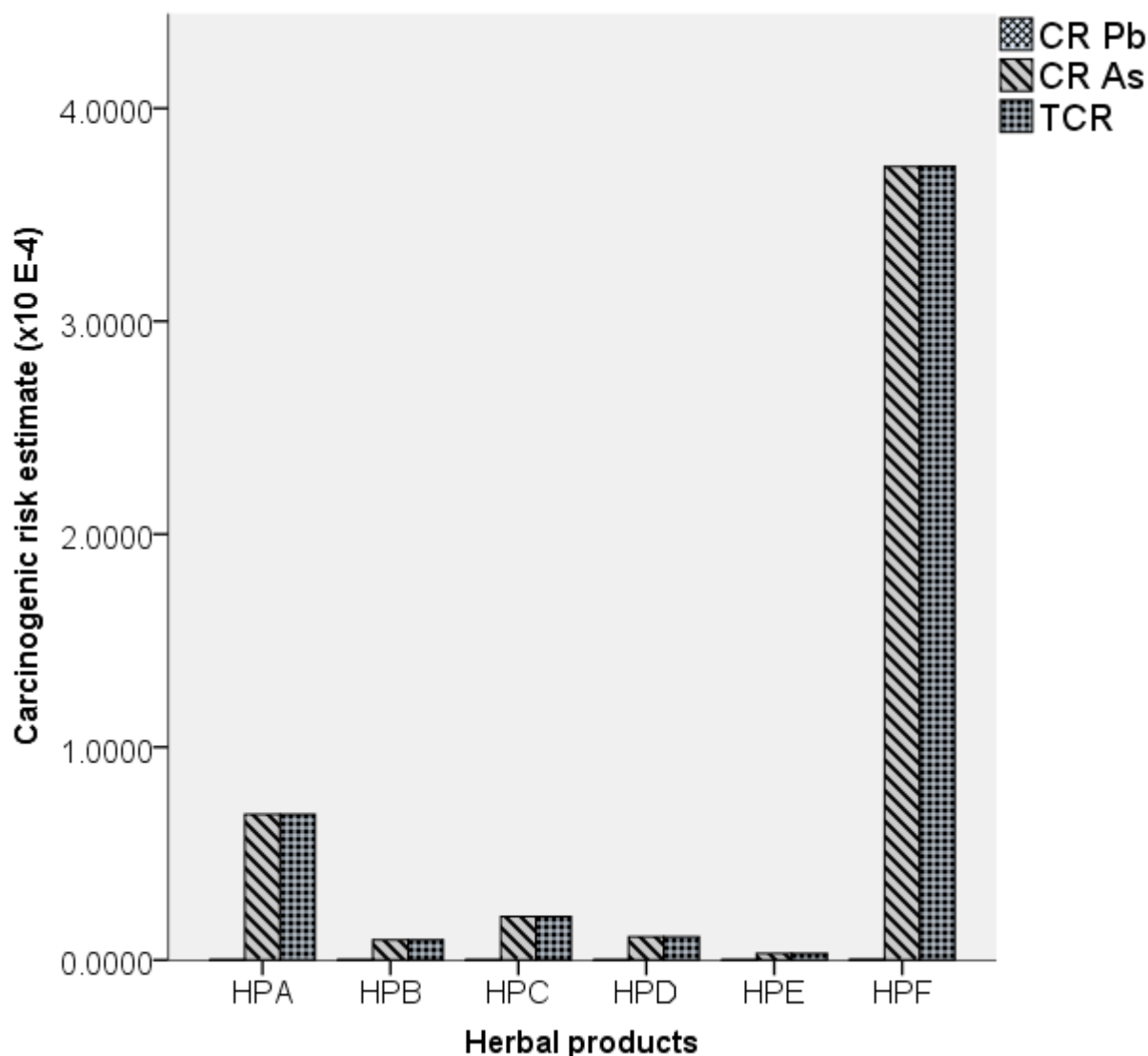
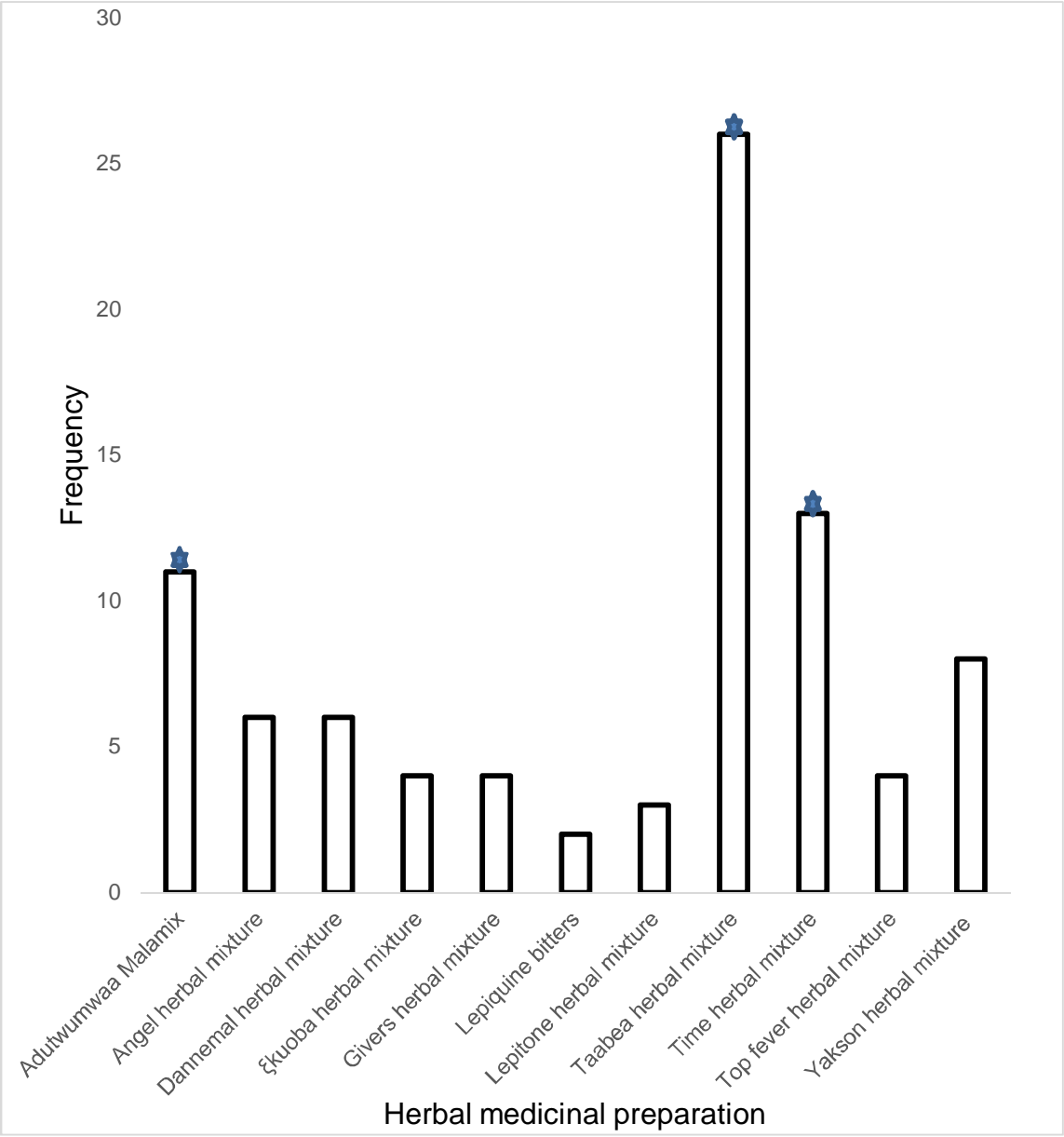


Figure 3: Estimated cancer risk (CR) for the herbal medicinal products HPA-F

The cancer risk (CR) values for herbal products A-F are all within the acceptable limit. The total cancer risk (TCR) as a result of the sum total of the individual cancer risk present by the carcinogenic metals per herbal preparation were also within the acceptable limit. It was observed that, the contribution of carcinogenic risk from As was much higher than contribution of CR from Pb in all the herbal products.

CR is for cancer risk. Total CR is for total cancer risk per herbal preparation which is the sum total of the risk from As and Pb in the herbal product.

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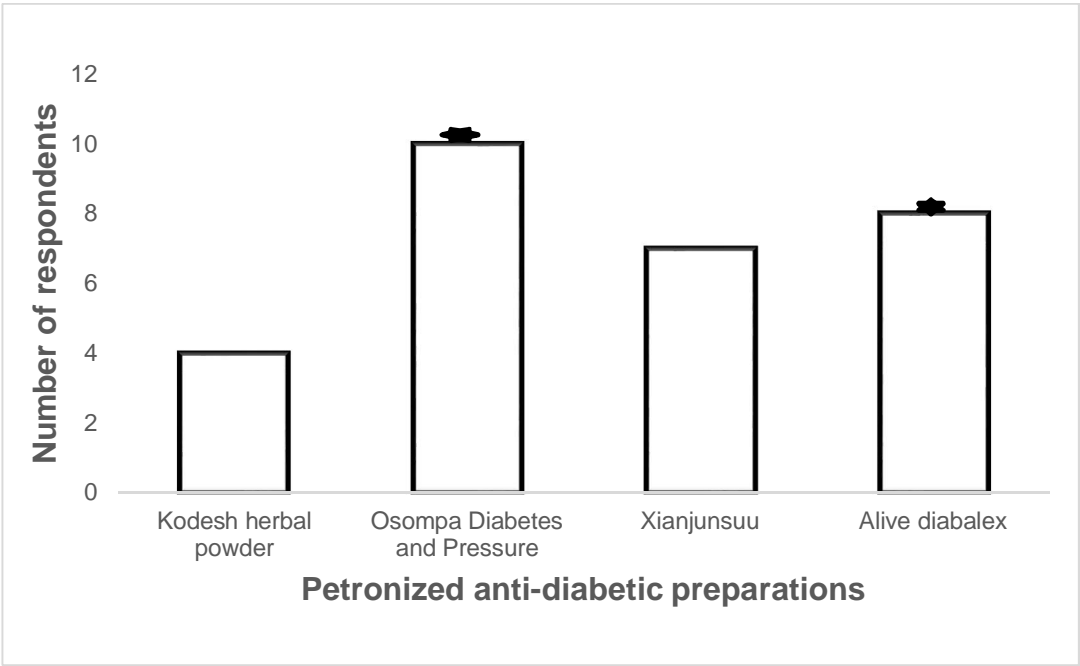


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532 Figure 4A: Commonly patronized antimalarial herbal medicinal preparations among surveyed
533 participants in the Kumasi metropolis of Ghana. The bars with the star represent the top-three most
534 patronized antimalarial herbal medicinal products selected for the study.

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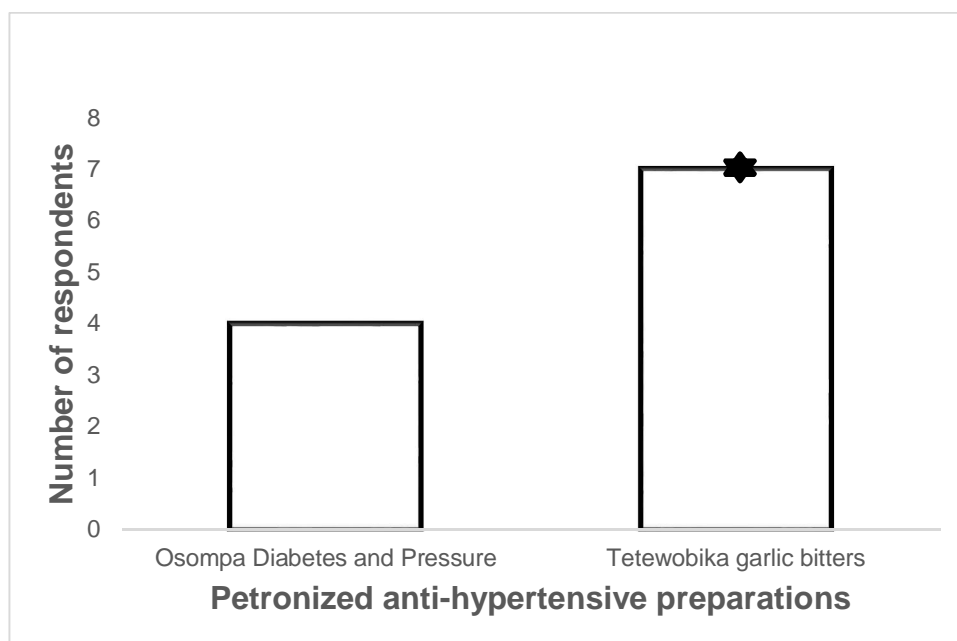


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539 Figure 4B: Commonly patronized antidiabetic herbal medicinal preparations among surveyed participants in
540 the Kumasi metropolis of Ghana. The bars with the star represent the top-two most patronized antidiabetic
541 herbal medicinal products selected for the study. Number of diabetic respondents was 29.

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546 Figure 4C: Commonly patronized antihypertensive herbal medicinal preparations among surveyed
547 participants in the Kumasi metropolis of Ghana. The number of respondents for antihypertensive
548 herbal preparations was 11. The bar with the star represents the top-one most patronized
549 antihypertensive herbal medicinal product selected for the study. The second most patronized
550 product ‘Osompa’ diabetes and pressure’ is used for the treatment of both diabetes and pressure and
551 has already been short-listed as an anti-diabetic preparation in this study.

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